Please replace paragraph [000195] with the following paragraph:

[000195] Both IC and i.v. delivery strategies resulted in the majority of radiolabel being deposited in the liver. Surprisingly, liver deposition was similar for both techniques, indicating significant recirculation for IC delivery. In addition, these results confirm the previous observation that the liver is the major organ of elimination with circulating bFGF binding to α-2-macroglobulin, which in turn is internalized by receptors on Kupffer. This result was duplicated for renal and lung deposition. It is important to point out that bFGF was infused in the ear vein (above the diaphragm). However, this simulates i.v. delivery in patients where the port of entry would probably be an upper extremity vein bypassing the liver first pass mechanism. Therefore, IC delivery does not result in less systemic deposition, probably due to high recirculation.

In the Claims:

Please cancel claims 44 - 46 and 48 - 53, without prejudice and without limitation of Applicant's right to pursue the subject matter of these claims in subsequent continuation or divisional applications.

REMARKS

It is respectfully requested that the above-identified application be reconsidered in view of the following Remarks, and the claims as amended. It is submitted that no new matter has been introduced by these amendments. It is further submitted that the claims, as amended, are in a condition for allowance, which action is earnestly requested.

Status of the Claims

As filed, the instant application contained claims 1 - 15; Claims 16 - 53 were added by Preliminary Amendment. The present Amendment has cancelled claims 44 - 46 and 48 - 53. Thus, claims 16 - 43 and 47 remain for

consideration. Claims 25 - 34 were withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b), as being drawn to a non-elected invention.

Objections to the Specification

The Action has stated a number of objections to the specification. The bulk of these have been addressed by the specific amendments to the specification as detailed above. In paragraph 6, the Action objected to the specification due to the fact that the specification was apparently missing pages, 45, 50, 57, and 65. The allegedly missing pages consequently created disruptions in the text of the specification due to incomplete sentences. These specific discontinuations have been addressed by the above amendments to the specification.

Despite these amendments to the specification, Applicant submits that the application, as filed, contained all of the pages of the specification (see copy enclosed), including those indicated in the Action as being missing. Applicant's representative has obtained a copy of the application from the USPTO, which copy confirms that the application in the current file is missing the pages specified in the Action. However, this copy further reflects the fact that, at some time after receipt of the original application, the USPTO subjected the pages of the application to optical scanning. This is presumed from the numerical coding of each page with the application number and date of filing on the left margin. Applicant respectfully submits that the application as filed was complete and that the pages identified as missing were lost by the USPTO in connection with the scanning process. This is further substantiated by review of the published PCT counterpart (a copy of which is enclosed) to the US application, which published application contains all of the pages as originally submitted. Both the US and PCT applications were prepared to be identical and were submitted simultaneously on April 6, 2001. The only differences between the two applications are in the respective cover pages, which pages reflect the submission of the applications to different examining authorities.

As an alternative to amendment to the paragraphs where sentence fragments were created by the missing pages set forth above (relating to paragraphs [000111], [000114] and [000168]), Applicant hereby requests that missing pages 40, 45, 50, 57, and 65, copies of which are submitted herewith, be entered into the case. Support for these pages arises from the application as filed, before the USPTO lost the pages in question, as further supported by the identical specification filed with the PCT counterpart to this application (copy enclosed). Consequently, no new matter would be added.

Claim Rejections

The Action has rejected claims 16 - 24, 35 - 43, and 47 under 35 U.S.C. § 112, ¶ 1 as allegedly containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 44 - 46 and 48 - 53 were rejected under 35 U.S.C. § 112, ¶1, allegedly because the specification, while being enabling for administration of angiogenic growth factors and localized delivery, does not reasonably provide enablement for any growth factor or for systemic delivery of same. Due to cancellation of these claims without prejudice by the instant Amendment, the stated rejection is rendered moot.

Claims 44 - 46 and 48 - 53 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Merck & Co. Inc. (GB 2 332 373A). Please note again that Applicant has canceled claims 44 - 46 and 48 - 53, without prejudice, reserving all rights to pursue these claims in continuation or divisional filings, thus rendering moot the stated rejection.

Rejections under 35 U.S.C. § 112, ¶ 1

Claims 16 - 24, 35 - 53 and 47 stand rejected under 35 U.S.C. § 112, ¶1. Applicant respectfully traverses such rejection.

A patent speaks to a person of ordinary skill in the art, not the general public. *W.L. Gore & Assoc. v. Garlock, Inc.*, 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983). In view of the state of the art concerning the pulmonary drug delivery of growth factors, and knowledge attributable to one of ordinary skill in that art area, the Action's position that a "large quantity of experimentation" is needed to practice the claimed invention is respectfully traversed. Contrary to the assertions in the Action, formulation of therapeutically active drug species for pulmonary delivery is well known in the art. See, for example, U.S. Patent No. 5,915,378 to Lloyd, *et al.*, "Creating an Aerosolized Formulation of Insulin." In the Lloyd *et al.* patent, the applicants describe a formulation for the inhalation of insulin, which delivers a therapeutic protein to the patient *via* the intrapulmonary route. In addition, those skilled in the art would recognize that specific information regarding formulations for aerosolized delivery devices can be found within *Remington's Pharmaceutical Sciences*, A.R. Gennaro, Ed.

Moreover, U.S. Patent No. 5,254,330 to Ganderton, *et al.* (and references cited therein) describes crystalline sugar carriers for dry powder formulations that are amenable for use with a wide variety of pharmacological agents, particularly for biologically active agents not conveniently administered to patients by other routes. Examples of the active agents that can be used with these carriers include growth factors.

Typically, the active agents in powder inhalers are lyophilized and finely divided into smaller particles. The active agent is generally used with a larger sized carrier particle, up to 1000 microns in diameter (preferably between 30-250 microns). The carrier particle may be any non-toxic material which is chemically inert. Though the Ganderton reference teaches a crystalline sugar carrier, as would be known by one of skill in the art, other common carriers include inorganic salts, organic salts, organic compounds, mono-, di-, and polysaccharides. See Franco Declaration, ¶ 11; and U.S. Patent No. 4,409,237. It is therefore known in the art that growth factors and related proteins can be readily formulated for dry powder inhalation using one of the common carriers.

Moreover, it is known to those skilled in the pharmaceutical formulation art that biologically active agents, particularly biological macromolecules, including proteins and peptides, are generally combined with other additives or carriers that can serve a variety of functions. See Franco Declaration, ¶ 12. For instance, the additives or carriers can be combined with the active agent powder to dilute the powder to an amount suitable for delivery; to facilitate the *in vivo* release of the active agent; to improve the properties of the preparation; for stability; to adjust the pH; or to improve the taste of the drug. See U.S. Patent No. 6,436,902 to Backstom. Examples of potential additives include mono-, di-, and polysaccharides, sugar alcohols and other polyols, such as lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol, and starch. The identity and amount of additive desirable would be easily determined by a person skilled in the art according to particular circumstances. See U.S. Patent No. 6,436,902.

In response to the Examiner's question of how the growth factor will reach the desired organ, *i.e.*, the heart, it is known to those skilled in the art that dry powder formulations of drugs are transported not only into the lungs, but into the circulatory system of a patient. See Franco Declaration, ¶¶ 6-7. One skilled in the area of pulmonary drug delivery systems would recognize that upon inhalation, air passes through the trachea, which branches into successively smaller tubes (constituting the bronchial network), and which eventually reaches tiny air sacs known as alveoli. See ¶ 7 of Franco Declaration. The large surface area of alveoli allows oxygen to be distributed deep within the lung tissue, from which oxygen passes into the bloodstream via an extensive capillary network. Drug therapies are thusly distributed to the target tissues via the bloodstream.

For a specific example, U.S. Patent No. 5,915,378 describes typical dry powder formulations for the administration of insulin, including an alveolar surfactant protein effective to enhance the transport of the liposomes across the pulmonary surface and into the circulatory system of the patient.

U.S. Patent No. 5,006,343 to Benson, *et al.*, "Pulmonary administration of pharmaceutically active substances," describes formulations that aid in the delivery of a variety of therapeutic agents. The liposomes and formulations described therein facilitate the pulmonary administration of active substances for both lung-specific therapeutic agents as well as for therapeutic agents intended for other organs, which are reached after the therapeutic agent enters the circulatory system. The liposome-forming composition described in the Benson disclosure can thus be coupled with pharmaceutically active substances, including, but not limited to insulin, growth hormones, other peptide hormones, thrombolytics, fibroblast growth factor, calcitonin, vasopresin, renin, thyroid stimulating hormone, and others for the delivery of pharmaceutically active substances across pulmonary surfaces.

A patent need not teach and preferably omits what is well known in the art, *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F2d 1367, 231 USPQ 81 (Fed. Cir. 1986). Even if the practice of the invention, *i.e.*, the formulation of the therapeutic agents might require some experimentation, enablement is not precluded, provided that the experimentation is not undue. *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991); *DeGeorge v. Bernier*, 768 F.2d 1318, 226 USPQ 758 (Fed. Cir. 1985). As evident in the specification, the state of the art, and from the Franco Declaration, the present invention is readily amenable to dry powder inhalation formulations.

The Action alleges lack of guidance in the specification in overcoming systemic angiogenesis. However, it is known by those in the field that VEGF activity is stimulated in oxygen-free environments. (*See* Josko, *et al.*, Vascular endothelial growth factor (VEGF) and its effect on angiogenesis, *Med. Sci. Monit.* **2000**; 6(5), 1047-1052 and references therein). See ¶¶ 14-15 of Franco Declaration. Hypoxia (lack of oxygen) is a known factor that stimulates both secretion of protein growth factors and receptors for growth factors such as, for example,

VEGF. See ¶ 14 of the Franco Declaration. For VEGF, the response of VEGF receptors to hypoxia varies from selective stimulation of Flt-1 to inhibition of Flk-1/KDR. *In vivo* studies in rats have demonstrated that in an oxygen-free environment, there is a quantitative increase in VEGF and Flt-1 receptors in hepatocytes. (See Josko, *et al.*, "Vascular endothelial growth factor (VEGF) and its effect on angiogenesis," *Med Sci Monit.*, **2000**; 6(5); 1047-1052).

In contrast to the hypoxic environment normally encountered in damaged heart tissue (the usual site of administration of protein growth factors such as FGF and VEGF during highly invasive open heart surgery) the nasal cavity, throat and lungs are highly oxygen effused and therefore do not constitute an environment that would lead to significant VEGF or FGF activity. It is therefore unlikely that systemic angiogenesis (*e.g.*, in the nasal cavity, throat and lungs) would be an obstacle.

Moreover, the angiogenesis factors of the formulations of the present invention would be inhaled directly into the lungs and then from there travel a very short path within the patient's circulatory system to reach the target organ, the heart, where growth factor receptors, the presence of which is elevated due to the low oxygen condition within damaged heart tissue, effectively insure the targeted delivery of the active species. To ensure that there are no side effects in the nasal cavity/mouth, the patient can immediately rinse the mouth area after inhalation. As presented in ¶ 16 of the Franco Declaration, once inhaled into the lungs, the angiogenic factors would be delivered to the left atrium, left ventricle of the heart, and then be available for an effect on the coronary vasculature with targeted delivery assured by high levels of secretion of appropriate receptors in the oxygen-starved damages heart tissues. As opposed to the direct inhalation of the drugs, the intravenous route has a much longer pathway prior to being available to the coronary vasculature. See Franco Declaration.

In summary, the Action contends that the instant disclosure is inadequate to enable a pulmonary route of delivery for the growth factors of the present

invention. It is submitted that dry powder inhalation formulations have been extensively investigated and the results of those studies have received considerable exposure in the relevant literature available to those skilled in the art. Those skilled in the art would thus know how to formulate and how to administer the formulation to the patient for the indicated treatment without undue experimentation. The Declaration of the instant inventor, Dr. Franco, attests to the viability of the above technique in the present invention. In total, it demonstrates that the present invention is enabled for pulmonary delivery, based on the knowledge and skill of those skilled in the art. Therefore, the Examiner's rejections are respectfully traversed.

CONCLUSION

It is respectfully submitted that all of the claims now remaining in this application are in condition for allowance, and such action is earnestly solicited.

If after reviewing these remarks, the Examiner believes that a telephone or personal interview would facilitate the resolution of any remaining matters the undersigned attorney may be contacted at the number below.

Respectfully submitted,

Date: 21 January 2003

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Amendments to the Specification

[00044] **Bioavailability** After the aerosolized drug reaches the deep lung, it must be absorbed with high enough bioavailability to make the system practical. As early as 1925, insulin inhalation for the treatment of diabetes was shown to work in humans, but the bioavailability was low (<3%). More recently, several inhalation studies comparing insulin administration by aerosol inhalation (using cumbersome devices) and by subcutaneous injection for the reproducibility of dosing have shown that the variability in glucose response to the two methods was equivalent. Bioavailability in more recent studies with aerosol insulin was up to 25%, supporting the use of such a method of administration. Laube, B. L.; Georgopolos, A.; Adams, G. K. *J. Am. Med. Assoc.* **1993**, *269*, 2106. Insulin administered by oral inhalation effectively normalized diabetic patients' plasma glucose levels without adverse effects. Numerous patents have issued, directed to methods, formulations and devices for the oral administration of insulin via inhalation therapy. See, for example, U.S. Patents Nos. [%]5,952,008; 5,858,968; and 5,915,378, the disclosures of which are hereby incorporated specifically by reference.

[000111] Fifteen minutes of global ischemia followed by twenty minutes of reperfusion resulted in prolonged ventricular dysfunction characterized by reduced levels of LVP generation as well as significant decreases in dP/dt_{max} and dP/dt_{min}. Pretreatment with rFGF-2 significantly improved the extent of recovery of LVP compared with control (untreated) hearts (83 ± 5 vs. 61 ± 6%) and equally significant preservation of dP/dt_{max} and dP/dt_{min} (86 ± 3 vs. 65 ± 6% and 85 ± 5 vs. 60 ± 5%, respectively. Stunning in hearts perfused with either NOS inhibitor by itself was not different from that in control hearts. Functional recovery of LVP in untreated control hearts (61 ± 6%) was not significantly different from that in hearts perfused with either L-NAME alone (59 ± 9%) or L-NIL alone (57 ± 6%). Depression of dP/dt_{max} and dP/dt_{min} (65 ± 6 and 60 ± 5%, respectively) in untreated hearts was similar to that in hearts perfused with L-NAME alone

(60 ± 9 and 55 ± 8%, respectively) and hearts perfused with L-NIL alone (57 ± 9 and 67 ± 4%, respectively).

[000114] *Ischemia and reperfusion.* The hearts were subjected to no-flow ischemia for 15 min. The organ bath was evacuated of its oxygenated solution and refilled with nitrogen-saturated perfusate. Pacing was maintained during ischemia. LV pressure was monitored throughout ischemia and reperfusion. All hearts ceased to contract within 3 min. The time for LVP to fall to 10% of baseline (T_{LVP10}) was measured to quantify differences in LV function during early ischemia. Mean ischemic Ca_i^{2+} was calculated as the mean Ca_i^{2+} recorded from the 2nd through the 14th minute of ischemia. Contracture was defined as an abrupt and sustained rise in intraventricular pressure above 4 mmHg. Contracture time was measured as the time from the onset of ischemia to the onset of contracture. At the end of 15 min of ischemia, the nitrogen-saturated bath was replaced by the original bath maintained at 30°C. Flow was recommenced. Mean Ca_i^{2+} during early reflow was calculated as the mean of the peaks of Ca_i^{2+} recorded during the 1st minute of reperfusion. After 20 min of reperfusion, Ca_i^{2+} and functional parameters were again measured.

[000119] *Quantification of NOS Gene Expression* To determine NOS2 and NOS3 mRNA levels in FGF-2-treated compared with control hearts, 30 cycles of RT-PCR were performed on equal amounts of total RNA from six control and six rFGF-2-treated hearts using primers corresponding to human NOS3 and NOS2 sequences. For NOS3, primers were as follows: 5' (sense), 5'-CAGTGTCCAACATGCTGCTGGAAATTG-3' (bases 1,050-1,076) (SEQ ID NO: 1); antisense, 5'-TAAAGGTCTTCTTGGTGATGCC-3' (bases 1,511-1,535) (SEQ ID NO; 2). For NOS2, primers were as follows: 5' (sense), 5'-GCCTCGCTCTGGAAAGA-3' (bases 1,425-1,441) (SEQ ID NO: 3); antisense, 5'-TCCATGCAGACAACCTT-3' (bases 1,908-1,924) (SEQ ID NO: 4). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) mRNA was amplified from the same amount of RNA at the same time to correct for variation between

different samples. The PCR products, separated on 1% agarose gels, were scanned and quantitated using Image-Quant software (Molecular Dynamics).

[000168] This randomized, double-blind, placebo-controlled study of bFGF in patients undergoing CABG demonstrates the safety and feasibility of this mode of therapy in patients with viable and ischemic but unrevascularizable myocardium. These results warrant a larger multicenter trial to assess the clinical benefit of this combination approach to myocardial revascularization, which is currently under way.

[00181] **Acute Hemodynamic Studies** In five additional dogs of either sex (weight, 19 to 22 kg), we compared the effects of intracoronary bFGF on coronary hemodynamic parameters with those of temporary coronary occlusion and intracoronary NTG. The studies were performed with the use of a standard open-chest model in which the LAD was isolated and instrumented with a Doppler flow probe to measure blood flow (Crystal Biotech). A 2F catheter was advanced retrogradely via a small proximal branch of the LAD into the left main vessel for administration of drugs. Blood flow responses after 10- and 20-second periods of LAD occlusion and after incremental doses of intracoronary NTG (1, 10, and 100 µg) were recorded to confirm the presence of coronary vascular reactivity. Incremental doses of intracoronary bFGF (1, 10, and 100 µg) were then given, and coronary flow responses were measured. bFGF (buffered as described above) and NTG solutions were prepared in 1 mL of normal saline just before administration and were given as boluses over 20 seconds. Blood pressure, heart rate, and ECG were monitored continuously throughout the procedure. Coronary vascular resistance (CVR) was calculated according to the formula:

$$CVR\ (\text{mmHg}\bullet\text{mL}^{-1}) = \textit{mean aortic pressure}\ (\text{mm Hg}) \times 1/\text{coronary flow}\ (\text{mL/min})$$

[000191] **Cardiac Deposition.** Total specific activity (1 h) was 0.88 ± 0.89% for IC and 0.26 ± 0.08% for i.v. administration ($p = .12$) and decreased to 0.05 ± 0.04% ($p = .05$, compared with 1 h values) and 0.04 ± 0.01% ($p < .001$, compared with 1 h values) at 24 h, respectively. There were no differences between epicardial and endocardial deposition for both IC delivery;

the results were pooled for further analysis. For IC delivery, LAD territory activity per gram of tissue (1 h) was 0.01 ± 0.007% and 0.008 ± 0.008% for normal and ischemic animals, and at 24 h dropped to 0.0005 ± 0.0009% (20-fold reduction) in nonischemic animals and 0.0008 ± 0.0005% (10-fold reduction) in ischemic animals. For i.v. delivery, 1-h LAD territory activity per gram of tissue was 0.003 ± 0.001% (3-fold reduction, p = .2, compared with IC) and 0.002 ± 0.0009% (4-fold reduction, p = .3, compared with IC) for normal and ischemic animals, and at 24 h dropped to 0.0004 ± 0.0001% (7.5-fold reduction) in nonischemic animals and 0.0004 ± 0.0004% (5-fold reduction) in ischemic animals, respectively. For 1-h LCX myocardial deposition, IC and i.v. deliveries resulted in a specific activity per gram of tissue of 0.008 ± 0.004% and 0.003 ± 0.001% (2.6-fold reduction, p = .09) in normal animals and 0.01 ± 0.007% and 0.003 ± 0.001% (3.3-fold reduction, p = .2) in ischemic animals, respectively. At 24 h, LCX deposition for IC and i.v. delivery dropped to 0.0006 ± 0.0008% and 0.0005 ± 0.0002% in normal animals and 0.0006 ± 0.0006% and 0.0004 ± 0.0004% in ischemic animals, respectively. For all groups, RCA myocardial distribution was similar to LAD and LCX distribution for i.v. administration. However, for IC delivery, RCA myocardial deposition was significantly lower than LAD or LCX myocardial deposition, because the radiolabel was infused in the left main coronary artery. Finally, for IC delivery, LCX/LAD territory activity was 79% and 154% for nonischemic and ischemic animals at 1 h and 116% and 75% for nonischemic and ischemic animals at 24 h, respectively. Intravenous administration resulted in an LCX/LAD activity of 97% and 100% for nonischemic and ischemic animals at 1 h and 123% and 98% for nonischemic and ischemic animals at 24 h, respectively.

[000195] Both IC and i.v. delivery strategies resulted in the majority of radiolabel being deposited in the liver. Surprisingly, liver deposition was similar for both techniques, indicating significant recirculation for IC delivery. In addition, these results confirm the previous observation that the liver is the major organ of elimination with circulating bFGF binding to α-2-macroglobulin, which in turn is

internalized by receptors on Kupffer. This result was duplicated for renal and lung deposition. It is important to point out that bFGF was infused in the ear vein (above the diaphragm). However, this simulates i.v. delivery in patients where the port of entry would probably be an upper extremity vein bypassing the liver first pass mechanism. Therefore, IC delivery does not result in less systemic deposition, probably due to high recirculation.

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